PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Attorney Docket No. 006420.00004)

In re U.S. Patent Application of	)	
	)	
Dharmadhikari, et al.	)	
	)	Examiner: Chris E. Simmons
Application No. 10/526,285	)	
	)	Art Unit: 1612
Filing Date: March 2, 2005	)	
	)	Confirmation No. 4683
For: PHARMACEUTICAL COMPOSITION OF METAXALONE WITH ENHANCED ORAL BIOAVAILABILITY	)	

DECLARATION OF DR. NITIN DHARMADHIKARI UNDER 37 CFR § 1.132

Commissioner for Patents
P.O.Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Nitin Bhalachandra Dharmadhikari, do hereby declare as follows:

2. I am a citizen of India and reside in Mumbai, India.

3. I hold a doctorate degree in Pharmacy from Nagpur University, India.

4. I presently hold the position of Vice President, Formulation Development, at **SUN PHARMA ADVANCED RESEARCH COMPANY, LTD.,** the assignee of the present application, where I am responsible for, among other things, formulation development activities. In particular, my experience includes work on solid orals and new drug delivery systems in orals. I have been actively involved in such type of work for twenty years. My curriculum vitae is attached as Annexure I. I am a co-inventor of the present application.

5. I have reviewed the examiner's objections in the final office action mailed December 7, 2009. I have also read the Amendment and Response to the final Office Action mailed December 7, 2009, and I submit this Declaration to accompany and support the Amendment and Response. I have reviewed the prior art references cited in the final Office Action. I believe that a person skill in the art, after reading Scaife et al (US Patent 6,407,128), would believe that Scaife et al teaches that the extent of absorption of metaxalone is increased and that the rate of absorption of metaxalone is decreased when the composition is given with food as compared to given on an empty stomach.

This may be because metaxalone is a hydrophobic drug with log P value of 2.42. In contrast to this theory, the inventors of the present invention have found that a specific sized micronized form of metaxalone when administered on an empty stomach, provides an increase in both the extent and rate of absorption. At the time of invention, this finding was indeed surprising, unexpected and unpredictable.

To elaborate, the claimed invention provides the unexpected benefits of an increase in both the extent and rate of absorption of metaxalone when administered without food to a patient on an empty stomach. The benefits of the present invention are indeed unexpected because the data in Scaife suggest that the extent of absorption and the rate of absorption are inversely correlated when one tries to increase bioavailability of a drug. *See* Table II b Col. 5 of Scaife. As previously noted in the Response mailed June 3, 2009, Table II b Column 5 of Scaife states that the Scaife composition when administered to a patient without food has a faster Tmax (Time to reach the peak plasma level of 3.32 hours) and lower AUC numbers (i.e., extent of absorption) than the same composition when administered to a patient with food (Tmax time is 4.29 hours). Thus, Scaife teaches that while the AUC numbers are greater when the Scaife composition is given to a patient with food than without food, it takes longer to reach peak levels (i.e., rate of absorption) when the Scaife composition is given to a patient with food than without food.

Although Scaife (in column 6, lines 36-37 and lines 45-47) states that the composition has a higher rate and extent of absorption, such conclusion is incorrect in view of an increase in Tmax upon administration with food. Tmax is a parameter closely related to the rate of absorption and may be used as a simple measure of rate of absorption. (*See* Remington's

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Pharmaceutical Sciences", 18th Edition, Mack Publishing Company, Easton, Pennsylvania, 1990, page 1455, submitted in an Information Disclosure Statement filed on October 13, 2006).

Generally, Tmax is related to the rate constant of absorption k_a by the equation:

$$Tmax = \frac{2.303}{k_a - K} \log \frac{k_a}{K}$$

K is the rate constant of elimination of drug from the body, and is unaffected by the presence of food. Therefore, changes in Tmax are related to changes in apparent rate constant of absorption.

On the other hand Cmax is given by the equation:

$$Cmax = \frac{F X_0 e^{-KTmax}}{V}$$

where F is the extent of absorption, X_0 is the dose, V is the volume of distribution, and Tmax the time to peak plasma concentration. (*See* Milo Gibaldi et al., pg 37-38, Equations 1.106 and 1.110, submitted as Exhibit B of the Response dated July 2, 2007).

Therefore, Cmax is dependent on both extent (F) and rate of absorption, i.e., Tmax. An increase in Cmax without a decrease in Tmax may thus be only due to an increase in the extent of absorption, i.e., F. For further background generally regarding the rate and extent of absorption, see Bioavailability and Bioequivalence: General Concepts and Overview, by Prof Richard Bergstrom et al. of Indiana University, posted on the net at: http://medicine.iupui.edu/clinical/F813_spring2006/Q_ClinicalPKF813Lecture16A07March2006BioavailabilityandBioequivalencerevised.pdf, (submitted as Exhibit C of the Response dated July 2, 2007).

On the other hand, Table 8 of the present application shows that a micronized form of metaxalone exhibits both a decrease in Tmax (i.e., an increase in the rate of absorption) and an increase AUC numbers (i.e., an increase in the extent of absorption) over the Skelaxin composition (i.e., the Scaife composition) when those compositions are administered to patients without food. This is unexpected in view of the teachings of Scaife that increasing the extent of absorption comes by administering the Scaife composition with food also results in an increase

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in Tmax, i.e., a decrease in the rate of absorption. The Office Action does not rebut these arguments that the Applicants made previously.

6. There is additional evidence which confirms the surprising effects of the present invention. A three way cross over study was conducted (Aug 2002), wherein relative bioavailability of the composition according to the present invention was determined after the composition was administered in the fed condition and on an empty stomach. In the third arm, the human volunteers were given Skelaxin® (the commercial form of drug disclosed in Scaife et al) on an empty stomach. The details of the composition according to the present invention are given below:

Table 1: composition subjected to three-way cross over bioavailability study

Ingredients	**mg/tablet**	**% w/w**
Metaxalone (micronized)	400.0	84.21
Colloidal silicon dioxide	8.0	1.68
Hydroxypropyl methyl cellulose (low viscosity)	15.0	0.84
Iron oxide red	0.3	0.063
Pregelatinzed starch	15.0	3.16
Sodium lauryl sulphate	0.6	0.13
Hydroxypropyl methyl cellulose (low viscosity)	2.5	0.53
Sodium starch glycolate	16.0	3.37
Microcrystalline cellulose	21.1	4.46
Collidal silicon dioxide	2.0	0.42
Magnesium stearate	5.5	1.16

Pregelatinized starch, colloidal silicon dioxide, low viscosity Hydroxypropyl methyl cellulose and iron oxide red were mixed together and sifted through ASTM # 40 screen. To the screen mixture metaxalone was added. Sodium lauryl sulphate was dissolved in water and added to the blend with slow stirring. The mixture was granulated with Hydroxypropyl methyl cellulose (low viscosity) solution. The granules were dried, lubricated and compressed into tablets. The particle size distribution of the metaxalone used in the composition was D_{50}=3.46 μms, D_{10}= 1.48 μms and D_{90}=6.71 μms.

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Fifteen healthy male volunteers were enrolled for the study and fourteen of them completed the study. Subjects were made to fast overnight before dosing and for 4 hours thereafter. Subjects, who were tested under fed condition, were given a standard high fat breakfast before and after dosing and a high fat lunch, snacks and dinner during appropriate times. For fasting subjects, standard meals were provided at 4 and 8 hours after dosing and at appropriate times thereafter. Meal plans were identical for both the periods. All subjects were housed from approximately 12 hr before dosing until after the 24 hr blood draw. A washout period of 5 days between the doses was kept. Metaxalone in plasma was measured by HPLC-UV method. The pharmacokinetic data obtained is tabulated as follows:

Table 2: Ln transformed parameters of the comparative bioavailability study on empty stomach

Least square means						90 % confidence intervals	
Parameter	Units	Skelaxin®	Composition of present invention	Ratio [1]	CV (%)	Lower	upper
C_{max}	µg/ml	0.85	3.38	394.9	31.61	294.59	529.3
$AUC_{(o-t)}$	µg.hr/ml	5.29	12.95	244.9	17.81	188.05	318.87
$AUC_{(o-\infty)}$	µg.hr/ml	5.99	13.11	219.0	18.35	169.83	282.47
$T_{½}$	hr	5.24	1.69	32.23		23.92	43.43
T_{max}	hr	3.11	1.6	50.09		35.96	69.76

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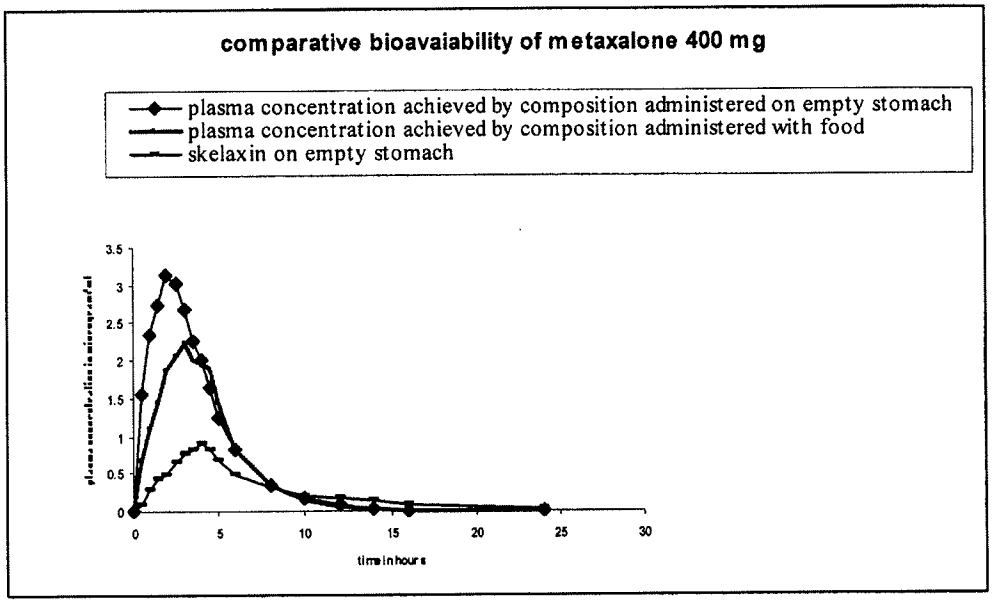

Figure 1: comparative bioavailability of metaxalone 400 mg – graph of mean plasma concentration Vs time in hours

7. The pharmacokinetic data given in Table 2, indicates that the composition of the present invention when administered on an empty stomach, showed AUC $_{(0-\infty)}$ almost 2-fold (% T/R Ratio= 219) higher than the AUC $_{(0-\infty)}$ achieved by Skelaxin® on an empty stomach. Further, the composition of the claimed invention showed a T_{max} value of 1.6 h as compared to T_{max} value of 3.11 h for Skelaxin® on an empty stomach. This implies that the composition of present invention when administered on an empty stomach achieved a relatively greater absorption and faster onset of action than Skelaxin®. The ratio of the 90 % confidence interval for the extent of absorption (AUC $_{(0-\infty)}$ = 169.83-282.47) was surprisingly far exceeding the upper limit of 125% (widely accepted by regulatory agencies including U.S FDA) indicating significant difference between the oral bioavailability of the test and reference products, composition of the present invention (test) and Skelaxin® tablets (reference) at the equivalent dose of metaxalone, when administered on an empty stomach. Even more surprising was the finding that the composition of the present invention, either administered in the fed condition (please refer to Figure 1), showed bioavailability higher than the Skelaxin® tablets when administered on empty stomach. The T_{max} and AUC $_{(0-\infty)}$ achieved by the composition of the present invention administered on an empty

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stomach was higher than Skelaxin® administered on empty stomach. Thus, composition of the present invention which uses micronized metaxalone, may be prescribed at a much lower dose compared to the usually prescribed 800 mg three to four times a day dose of Skelaxin®.

8. The three-way bioavailability study conducted did not include an arm wherein Skelaxin® was administered in the fed condition. Bioavailability values were extrapolated for Skelaxin® composition from the data presented in Table IIb of Scaife et al as if when it was given with food. The projected values were calculated by dividing a selected fasted Scaife value by the corresponding fasted Skelaxin value of the present study, then multiplying that quotient by the corresponding fed Scaife value. The projected values (#) calculated are tabulated in Table 3 below.

Table 3: Ln transformed parameters of the comparative bioavailability study of composition of the present invention given on fed condition Vs Skelaxin® on fed (values projected)

Least square means				
Parameter	Units	Skelaxin® # (R)	Composition of present invention (T)	T/R Ratio [1]
C_{max}	µg/ml	1.5	2.60	173
AUC $_{(o-t)}$	µg.hr/ml	6.4	10.20	159.4
$AUC_{(o-\infty)}$	µg.hr/ml	6.8	10.42	153.2
T_{max}	hr	4.01	2.45	

1: ratio of the parameters of test and reference; (#) = projected values

This projected value comparison supports the finding that the composition of the present invention, administered with food (please refer to Table 3), showed bioavailability higher than the Skelaxin® tablets when administered on fed condition (based on projected values).

9. I am of the opinion that the present invention offers a better patient compliance. The invention can be said to solve the problem of stringent requirement of administration of Skelaxin® tablets with food. That is, if a patient takes Skelaxin® by mistake on an empty stomach, or forgets to take with food, it is likely that sub-therapeutic metaxalone plasma levels

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would be achieved (please see figure 1). In contrast, if the patient by mistake administers or forgets and takes the composition of the present invention with food, still therapeutically effective metaxalone plasma levels would be achieved as per the data) (please see Figure 1).

10. As regards to the examiner's contention that the present invention is obvious over Liversidge and Martin in view of Scaife, I would also like to point out here that had 'micronization' or particle size reduction alone contributed to enhanced bioavailability, then bioavailability would have been enhanced much more in fed conditions than on empty stomach. But surprisingly and unexpectedly, I found that the composition of the present invention provided a supra bioavailability on empty stomach **rather than** when administered with food. This is indeed unpredictable because metaxalone is known to be a water insoluble drug with bioavailability problems. Knowing the background about metaxalone's properties, a person of skill in the art at the time of invention would not be in a position to predict even with a reasonable expectation of success that the micronized form of metaxalone would provide a grater rate and extent of absorption compared to the Skelaxin® when administered on empty stomach.

11. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonments, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 5/5/10

N.B. Dharmadhikari

Dr. Nitin Bhalachandra Dharmadhikari

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ANNEXURE I

BIO – DATA

Dr. N. B. DHARMADHIKARI
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Name : **NITIN BHALCHANDRA DHARMADHIKARI**

Present Address : D 602, Rakhee,
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Date of Birth : Fifth November Nineteen Sixty

Place of Birth : Nagpur (M.S.)

Marital Status : Married.

EDUCATIONAL QUALIFICATION

Examination	Name of Board University	Year of passing	Division	% of Marks
S. S. C.	Nagpur (India)	1975	1st	66%
H. S. C.	Nagpur (India)	1977	1st	62%
M. Pharm.	– do –	1983	1st	65%

Examination	Name of Board University	Year of passing	Division	% of Marks
Post Graduate Specialization Course	University of Ghent, Belgium	1988	-	-
Ph. D. (Pharmaceutics)	Department of Pharmacy, Nagpur University, Nagpur (India).	1989	-	-

WORKING EXPERIENCE

Period	Organization	Nature of Job
August 1999 - upto Date	Sun Pharma Advanced Research Company Limited, 17/B-Mahal Industrial Estate, Mahakali Caves Road, Andheri (E), Mumbai.	***Vice President – Formulation Development*** (April 2006 till date) ***Sr. General Manager – Formulation Development*** (April 2004 – April 2006) ***General Manager – Formulation Development*** (October 2001 – April 2004) ***Deputy General Manager – Formulation Development*** (August 1999 – October 2001) Responsible for Product development for filing of **Abbreviated New Drug Applications & New drug applications**

Period	Organization	Nature of Job
August1997 - August 1999	Ranbaxy Research Laboratories, Sector18, Udyog Vihar, Gurgaon, Haryana.	***Senior Research Scientist (Grade III Manager)*** Responsibilities included Development of dosage forms for Regulated Markets (USA, Western Europe)
October 1994 - July 1997	Dr. Reddy's Laboratories Ameerpet, Hyderabad.	***Manager (Formulation Development)*** Responsibilities included development and preparation **of Abbreviated New Drug Applications for USA .** Development process for highly regulated markets ensured good exposure to development of dosage forms, scaling up, process validation, cleaning validation and stability studies.
August 1993 – October 1994	Biological E. Ltd. 18/1 and 3 Azamabad, Hyderabad.	***Manager (Research and Development).***
November 1990 - August 1993	Biological E. Ltd. 18/1 and 3 Azamabad, Hyderabad.	***Dy. Manager (Research Development)***
November 1989 - November 1990	Pfimex International Ltd. 60/ A.I.D.A., Jeedimetala, Hyderabad.	***Manager (Research and Development)***
January 1985 - October 1989	Department of Pharmacy, Nagpur University, Nagpur.	***Research Fellow***

PROJECT AND RESEARCH WORK

1. Prepared a project report entitled ***"PROGRESS IN CHEMOTAXONOMY DURING THE YEARS 1970 TO 1979."***

2. Prepared a thesis entitled ***"DEVELOPMENT OF ACID DYE TECHNIQUE USING SOLOCHROME BLACK T, FOR ESTIMATION OF SOME DRUGS."*** For Degree of Master Of Pharmacy.

3. Prepared a thesis entitled ***"FABRICATION, FORMULATION AND EVALUATION OF MICROCAPSULES OF CIMETIDINE, SALBUTAMOL SULPHATE AND POTASSIUM CHLORIDE"*** for the degree of Ph.D. in Pharmaceutical Sciences.

4. Attended postgraduate specialization course entitled '***PHARMACEUTICAL TECHNOLOGY' organized by UNIDO and conducted by University of Ghent Belgium.*** Visited various Pharmaceutical Companies like Up-Jhon Belgium and MSD Amsterdam and London.

LIST OF RESEARCH PAPERS

1. Preparation and In-vitro evaluation of Salbutamol Sulphate Microcapsules. N. B. Dharmadhikari and S. B. Joshi.
   Presented at 9th Pharmaceutical Technology Conference, Veldhoven, Holland, 4th-6th April 1990.

2. Preparation and In-Vitro evaluation of Potassium Chloride Microcapsules. N. B. Dharmadhikari and S. B. Joshi.
   Poster presentation at 7th International Symposium on Microencapsulation Glassgow, Scotland, 2nd-4th April 1990.

3. Fabrication and evaluation of Nifedipine microcapsules. Manekar, S.B. Joshi, N.B. Dharmadhikari and D. S. Sheorey.
   Presented at 41st Indian Pharmaceutical Congress, Bombay.

4. Sustained action Nifedipine microcapsules. N.C Manekar,S.B. Joshi& N. B. Dharmadhikari
   Poster-presentation at 7th International Symposium on Microencapsulation, Glassgow, Scotland, 2nd-4th April 1990.

5. Microencapsulation of Nifedipine using coacervation phase separation technique. N. C. Manekar, N. B. Dharmadhikari and S. B. Joshi.
   Estern Pharmacist Vol. XXIII, No 393, September 1990 P. 137.

6. Microencapsulation of Nifedine using Melt Dispersion Technique, N. C. Manekar, N. B. Dharmadhikari and S. B. Joshi.
   IDMA Bulletin, August 7, 1990 No 27 P. No 516.

7. Preparation and In-vitro evaluation of Salbutamol Sulphate Microcapsules. N. B. Dharmadhikari and S. B. Joshi. And N. C. Manekar.
   Journal of Microencapsulation, 1991, Vol. No 4, 479-482.

8. Preparation and In-vitro evaluation of Cimetidine Microcapsules. N. B. Dharmadhikari and S. B. Joshi.
   Accepted for the oral presentation 42nd I.P.C., Manipal, 28th-30th December 1990.

Patents

Author / Co-author of following patents:

1. Controlled Release Coated Tablets Having Prolonged Gastric Retention, Publication info: US2008241238 (A1) - 2008-10-02
2. Oral Drug Delivery System, Publication info: US2008213381 - 2008-09-04
3. Stable Oral Pharmaceutical Composition, Publication info: US2008182887 - 2008-07-31
4. Coated Tablets Having Prolonged Gastric Retention, Publication info: EP1945189 - 2008-07-23
5. Oral drug delivery system, Publication info: US2008138410 - 2008-06-12
6. Pharmaceutical Dosage Forms Of Oxcarbazepine, Publication info: US2008138403 - 2008-06-12
7. Gastric Retention System, Publication info: US2008107732 - 2008-05-08
8. Oral Controlled Release Composition Containing Levetiracetam, Publication info: EP1909770 - 2008-04-16
9. Stable oral composition, Publication info: US2007053974 - 2007-03-08
10. Spaced drug delivery system, Publication info: EP1738751 - 2007-01-03
11. Oral pharmaceutical composition including paroxetine, Publication info: US2006216345 - 2006-09-28
12. Programmed drug delivery system, Publication info: US2006210633 - 2006-09-21
13. Stable compositions of bupropion or its pharmaceutically acceptable salts, Publication info: US2006204571 - 2006-09-14
14. Oral pharmaceutical composition, Publication info: US2006198885 - 2006-09-07
15. Pharmaceutical composition of metaxalone with enhanced oral bioavailability, Publication info: US2006167069 - 2006-07-27
16. Stable pharmaceutical formulations, Publication info: US2006045911 - 2006-03-02
17. Oral Pharmaceutical Composition, Publication info: WO2005115092 - 2005-12-08

18. Stable pharmaceutical composition, Publication info: US2005064029 - 2005-03-24
19. A Stable Pharmaceutical Composition, Publication info: WO2004087648 - 2004-10-14
20. Pharmaceutical Composition For Treatment Of Diabetes Mellitus, Publication info: WO2004082591 - 2004-09-30
21. Spaced drug delivery system, Publication info: US2004086562 - 2004-05-06
22. Time pulsed release composition, Publication info: US2004156900 - 2004-08-12
23. Oral osmotic controlled drug delivery system, Publication info: US2003219485 - 2003-11-27
24. Cardiotonic composition, Publication info: US2004048809 - 2004-03-11
25. Oral Controlled Release Pharmaceutical Composition Containing Metaxalone As Active Agent, Publication info: WO2004066981 - 2004-08-12